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(71) Applicants *(for all designated States except US)*: **NUTRALEASE LTD.** [IL/IL]; Ashkelon Technological Industries, South Industrial Zone, 78172 Ashkelon (IL). **YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM** [IL/IL]; Hi Tech Park, Edmond Safra Campus, Givat Ram, 91390 Jerusalem (IL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GARTI, Nissim** [IL/IL]; 9 Hachoresh Street, 97278 Jerusalem (IL). **ASERIN, Abraham** [IL/IL]; 5/10 Idelson Street, Ramot 03, 97665 Jerusalem (IL). **SPERNATH, Aviram** [IL/IL]; 1h Misho'l Bika't Yavniel Apt. 3, 44628 Kfar Saba (IL). **AMAR, Idit** [IL/IL]; Casali Institute, Hebrew University of Jerusalem, Givat Ram Campus, 91904 Jerusalem (IL).

(74) Agent: **REINHOLD COHN AND PARTNERS**; P.O.Box 4060, 61040 Tel Aviv (IL).

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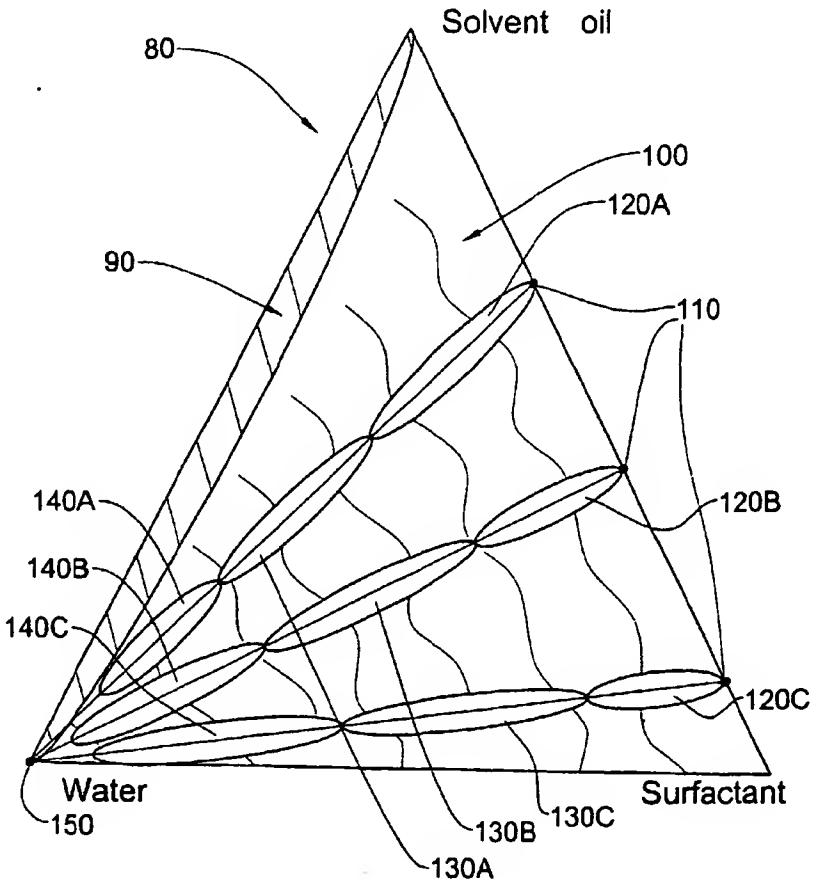
(54) Title: NANO-SIZED SELF-ASSEMBLED STRUCTURED LIQUIDS



(57) Abstract: The present invention relates to nano-sized self-assembled structured concentrates and their use as effective suitable carriers for transferring active components into the human body. The nano-sized self-assembled concentrates are composed of an aqueous phase, an oil phase, a surfactant, a co-solvent and co-surfactant. The formed nano-sized self-assembled structured concentrates may be in the form of an aqueous continuous phase, an oil continuous phase or a bicontinuous phase, and may thus be diluted to any desired extent in either oil or water maintaining their structure and the active material comprised within the nano-sized self-assembled structured concentrates.

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NANO-SIZED SELF-ASSEMBLED STRUCTURED LIQUIDS

FIELD OF THE INVENTION

This invention relates to nano-sized self-assembled structured concentrates and their use as carriers of active materials.

BACKGROUND OF THE INVENTION

Administering of active components into the human body requires the use of an appropriate vehicle for bringing an effective amount of the active component intact to the desired site in the human body. The desired site varies and it may be the blood stream, organs, cells etc. Active components usually are either oil-soluble or water soluble although their solubility in any of these environments may vary from good to poor. Active components that dissolve in oil or water very poorly pose a problem as to the route for their administration, transport and reaching their target. Furthermore, many chemicals that can serve as appropriate vehicles for such active compounds cannot be used in association with the human body, i.e. their use is unsafe or even hazardous. Constructing the appropriate vehicle and the desired efficient formulation, possess a challenge to developers of new medicaments.

Nutraceuticals, which are food supplements with health benefits, are commonly used as part of the daily diet. Nutraceuticals are vitamins, minerals, extracts of natural components (for example plants, flowers, roots or leaves), which are not medicaments, yet are believed to have a positive effect on the human body. They may have a long-term effect or an immediate effect and may be used for long treatment of chronically, yet not terminal diseases.

Nutraceuticals may be used for example in order to lower blood pressure, reduce cancer risk factors, regulate digestive tract system, strengthen immune systems, regulate growth, regulate sugar concentration in blood, lower cholesterol levels, serve as antioxidant agents and more. Antioxidants can donate electrons to quench and neutralize free radical oxygen molecules, which play an important role

in the initiation and promotion of atherosclerosis, cancer, cataract, arthritis and other degenerative diseases. Antioxidants can be (i) water-soluble such as vitamin C, simple phenols, polyphenols, bioflavonoids, rosmarinic acid, catechins, or (ii) oil-soluble (lipophilic) such as vitamin E, Co-Q_{10} (coenzyme Q_{10}, ubiquinone), vitamin D, vitamin B_{12}, carotenoids (lycopene, β-carotene, lutein), etc.

Examples of health benefits of some Nutraceuticals are: (i) Lycopene may protect against coronary vascular disease, reduce risk factors of prostate cancer, shrink tumors and reduce risk of upper digestive tract cancers. (ii) Lutein, in addition to its antioxidant activity, reduces the incidence of cataract, limits blue light damage and reduces age-related macular degeneration and (iii) Phytosterols are used for reducing cholesterol adsorption.

Although the use of nutraceuticals in capsules and tablets is abundant, their effect is frequently diminished or even lost since many of the nutraceuticals are not soluble in water, vegetable oils or food-grade solvents. Due to their low solubility, they cannot penetrate into the membrane therefore their bioavailability is very poor.

A common approach for constructing an appropriate vehicle for transporting nutraceuticals, medicaments, peptides or proteins is the use of microemulsions. In the microemulsion, the active compounds are not soluble but rather are solubilized. The general concept of solubilization of active components and its utilization may be found in the following review articles: **1.** Solans, C., Pons, R., Kunieda, H "Overview of basic aspects of microemulsions" *Industrial Applications of Microemulsions*, Solans, C., Kunieda, H. Eds.; Dekker: New York, (1997); **66**: 1-17; **2.** Dungan, S.R. "Microemulsions in foods: properties and applications" *ibid* 148-170; **3.** Holmberg, K. "Quarter century progress and new horizons in microemulsions" in *Micelles, Microemulsions and Monolayers*, Shah, O. Ed.; Dekker: New York (1998) 161-192; **4.** Garti, N., "Microemulsions, emulsions, double emulsions and emulsions in food" in *Formulation Science* (proceeding from formulation forum '97-association of formulation chemists) (1998) **I**, 147-219; **5.** Ezrahi, S., Aserin, A., Garti, N. *in Microemulsions–fundamental and applied aspects* Kumar, P. and Mittal, K.L. Eds. Marcel Dekker, Inc. New York (1999);

"Aggregation behavior in one-phase (Winsor IV) systems" 185-246; 6. Garti, N., Clement, V., Leser, M., Aserin, A. Fanun, M. "Sucrose esters microemulsions J. Molec. Liquids (1999) 80, 253-296.

US 6,063,762 describes a microemulsion for cyclosporin, consisting of oil, surfactant and a lipophilic solvent comprising of an ester of polycarboxylic acid and/or carboxylic acid ester of polyols. GB 588,298 describes a system for solubilizing lipoid soluble vitamins, comprising of polyalkylene oxide derivative of a partial fatty acid (more than C_{12}) and an ester of polyhydric alcohol, where the resulting solution is miscible in water or aqueous solutions. US 5,725803 discloses a new emulsifier for a water/oil system, comprising of phytosterol, 5-23 wt% C_{20-24}-alkyl alcohol and a mixture of C_{10-28}-fatty alcohols. WO 99/53,925 describes a composition comprising of phytosterols and lecithin which is dispersed in water by shaking, vortexing, sonicating or passing through a small orifice. WO 99/39,715 describes yet another system for solubilizing phytosterols by macromolecules, such as starch or saccharides.

Ultramicroemulsions and their use in pharmaceutical preparations are described in US 6,057,359 as an aqueous ultramicroemulsion, in US 5,536,504 for ultramicroemulsions containing xanthophyll esters, in US 6,180,661 where flavanol-glycoside per-esters are used for achieving an ultramicroemulsion, and in US 6,248,363.

SUMMARY OF THE INVENTION

The present invention is based on the findings of novel nano-sized self-assembled structured concentrates that can solubilize lipophilic compounds. The nano-sized self-assembled structured concentrates may be in the form of an aqueous continuous phase, an oil continuous phase or a bicontinuous phase. The novel nano-sized self-assembled structured concentrates may be diluted either in water or in oil to any desirable dilution while maintaining their structure. The nano-sized self-assembled structured concentrates may be used as effective suitable carriers for transferring active components into the human body.

Thus in one aspect the invention is directed towards nano-sized self-assembled structured liquid concentrates comprising of:

(i) water;

(ii) a polyol co-solvent selected from the group consisting of alcohols, polyalcohols, aldehydes, ketons, thiols, mono- and –di-saccharides;

(iii) at least one surfactant yielding a surfactant of hydrophilic nature;

(iv) co-surfactant selected from C_{2-16}-alcohols and C_{2-18} fatty acids; and

(v) oil phase being a solvent selected from the group consisting of paraffinic oils selected from hexane, heptane, octane, nonane, decane, undecane, dodecane, tridecane, tetradecane, pentadecane, hexadecane, heptadecane, octadecane; silicone oils; long chain fatty alcohols C_{5-18}, C_{2-12}-ketone, preferably C_{2-7}-ketone, C_{2-12}-aldehyde, preferably C_{2-7}-aldehyde, C_{2-24}-fatty acid or their esters, glycerol mono, di and tri-esters, terpene, terpin, terpinene, limonene, penta- or –tetracyclic triterpenic alcohols, sterol, alkylsterol, essential oil oleoresins, fat soluble lipidic vitamins, fennel oil, ginger oil, lavender oil, eucalyptus oil, anise oil, lemon oil, mandarin oil, peppermint oil, oregano oil, lime oil, tangerine oil, spearmint oil, triethyl citrate, ethyl oleate, ethyl caprylate, anisole, anisyl alcohol, benzyl acetate, benzyl alcohol, benzyl propionate, ethyl lactate, phenethyl alcohol. Terpenes and camphors selected from α-pinene, borneol, camphour, cineole, carvone, terpineol, menthol, menthone, thymol, geraniol, citral, terpinolene, hemonene, citronellal. Other natural flavoring materials selected from linalool, eugenol, vanillin. Synthetic flavoring materials selected from hexyl alcohol, hexyl aldehyde, benzaldehyde, cinnamic aldehyde, citronellyl butyrate, nerol, phelandrene, phenyl ethyl acetate, ethyl propionate, ethyl laurate, ethyl decanoate, ethyl butyrate, ethyl hexanoate, ethyl caprylate, brandy flavoring oil, apple flavoring oil, paprica flavoring oil, blackberry flavoring oil, blueberry flavoring oil, honey flavoring oil, licorice flavoring oil,

almond flavoring oil, maple flavoring oil, strawberry flavoring oil, watermelon flavoring oil; wherein said solvent may further comprise at least one co-solvent selected from fatty acids, fatty alcohols, sterols, terpins, terpenines, essential oils, vitamins.

In a yet further aspect the present invention is directed to a nanosized structured liquid concentrate for use as a suitable carrier for oil-soluble, oil non-soluble or water-soluble nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates. Thus the present invention is directed to nanosized structured liquid concentrates comprising therein oil soluble, oil non-soluble or water-soluble material selected from the group consisting of nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates. In a preferred embodiment the nutraceuticals are selected from lutein, lutein esters, β-carotene, lycopene, Co-Q_{10}, flax seed oil, fish oil, lipoic acid, phytosterols, α- and γ-polyunsaturated fatty acids, vitamin D, vitamin E, vitamin B_{12} or mixtures thereof

In a yet further aspect the present invention is directed to food products, medicaments or cosmetic preparations comprising the nano-sized self-assembled structured concentrates as an aqueous phase, as an oil phase or as a bi-continuous phase dilutable to any desirable extent.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, a preferred embodiment will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Figs. 1A and **1B** shows two phase diagrams of the prior art. **1A** shows a phase diagram having two small isotropic areas, one where the water is the continuous phase and one where the oil is the continuous phase, separated by a large two-phase region. **1B** shows a phase diagram where the oil/water consists essentially of two-phase and a single phase prevails only at the case where there is practically no oil.

Fig. 2 shows a general ternary phase diagram for a system composed according to the present invention. The 2-phase region is small and the single phase region is a continuous phase of both oil and water demonstrating the possibility of diluting.

Fig. 3 shows a ternary phase diagram for a system comprising a particular solvent according to the invention.

Figs. 4A, 4B, 4C and **4D** show the effect of dilution of lycopene in a system of the present invention. Figure 4A shows the ternary phase diagram indicating the ratio of the oil phase to the surfactant. Figure 4B shows the effect of aqueous-based dilution and solubilization of lycopene. Figure 4C shows the efficiency of the solubilization by the α-factor. Figure 4D shows various α-factors as a function of various surfactants.

Figs. 5A, 5B, 5C and **5D** show the effect of dilution of phytosterol in a system of the present invention. Figure 5A shows the ternary phase diagram indicating the ratio of the oil phase to the surfactant. Figure 5B shows the effect of dilution and solubilization of phytosterol. Figure 5C shows the efficiency of the solubilization by the α-factor. Figure 5D shows various α-factors as a function of various surfactants.

Figs. **6A, 6B, 6C** and **6D** show the effect of solubilization of lutein esters in two nano-sized structures of the present invention. Figure 6A shows the ternary phase diagram indicating the two possibilities of the ratio of the oil phase to the surfactant. Figure 6B shows the maximum solubilization reached in these two microemulsion systems. Figure 6C shows the solubility normalized to the surfactant in the two possible nano-sized structure systems. Figure 6D shows the solubility normalized to the oil in the two nano-sized structure systems.

Figs. **7A** and **7B** show the effect of solubilization of lutein ester compared to that of free lutein.

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described with reference to some non-limiting specific embodiments. The invention will first be illustrated in reference to the attached drawings to be followed by a more detailed description below. Turning to **Fig. 1**, there are shown two different phase diagrams (1A and 1B) of ternary systems comprising oil/water/surfactant according to the prior art. Such a ternary system forms microemulsions. As a function of the relative amounts of each of the three components one may achieve a two-phase or a mono-phase liquid concentrate comprising of the microemulsion where the boundaries of the stable phases depend on the relative concentration of each component. In **Fig. 1A** there is illustrated a ternary phase diagram **10** exhibiting a rather small isotropic stable water in oil (W/O) composition phase at **20** and an even smaller stable oil in water (O/W) phase at **30**. A two-phase region at equilibrium, at **35**, prevails at all other concentrations of the ternary system. **Fig. 1B** illustrates yet another ternary phase diagram **40** exhibiting a rather large two-phase concentrate (non-stable) **50** and small two-phase region at **60**. A one phase stable isotropic region exists at **65**. Turning to **Fig. 2**, there is displayed a general ternary phase diagram **80** describing the nano-sized self-assembled structured concentrates of the present invention. A rather small two-phase concentrate region **90** and a large stable one-phase at **100** region are present. A micellar concentrate of the nano-sized self-assembled structures exists at **110**, i.e. there is no aqueous phase. Adding a small amount of aqueous phase results in an oil continuous phase, which is actually water in oil (W/O) region at **120A**, **120B** and **120C** along the three dilution lines. Addition of an increasing amount of aqueous solution results in a bi-continuous region at **130A**, **130B** and **130C** along the three dilution lines. At the point where the amount of aqueous solution is greater than that of the oil phase there exists an aqueous continuous phase, which is actually an oil in water (O/W) region generally at **140A**, **140B** and **140C** along the three dilution lines. Direct micelles exist only at the extreme at **150**. It should be noted that along each concentration line as the concentration of the

surfactant increases, the oil continuous phase may decrease is size while the bicontinuous and water continuous phases may increase in size. Turning to **Fig. 3**, a ternary phase diagram **170** describing another nanosized-structured concentrate of the present invention is shown. The oil phase, which is the desired solvent for achieving a single-phase system, is α-tocopherol acetate. The aqueous system comprises of water and a co-solvent – propylene glycol. As shown, a major portion of the four-component system is in one stable region **180**, while only a minor portion **190** is a two-phase system. Phase diagrams, solubilization factors and efficiency of solubilization for lycopene, phytosterol and lutein in ternary systems according to the present invention are given in figures 4-6. In particular, **Fig. 4A** shows a phase diagram of a system for solubilizing lycopene, wherein the system is comprised of an aqueous phase comprising water/propylene glycol in a 1:1 ratio, an oil phase comprising of limonene/ethanol in a 1:1 ratio, and Tween 60 as the surfactant, where the ratio of the surfactant to the oil phase is 3:2 (indicated as the **64** line). It should be noted that the ratio between each of the components of the oil phase to the surfactant is 1:3. **Fig. 4B** shows the solubility capacity of lycopene (milligrams) in 1Kg of nano-sized self-assembled structured concentrate, where the maximum solubility is 450mg, i.e. maximum solubilization is 0.45% (wt) reached at the point where the aqueous phase is about 67% of the composition. As shown, upon further dilution with water, the solubilization of lycopene drops over the dilution factor. In case the system is diluted from 67% water to 80% water, the dilution factor (from inversion) is 80/67=1.19. The solubilization on the other hand decreases by a factor of 450/312.5=1.44. This indicates structural change in the nano-sized self-assembled concentrates. Turning to **Fig. 4C**, the efficiency of the solubilization in the described system is represented (α). The efficiency factor, α, is defined as lycopene/oil(wt/wt)X 100. As shown, the maximum solubilization on an oil base is 0.8 wt%. Thus the nano-sized structured system of the present invention succeeds in solubilizing lycopene up to 17.7 fold of the oil dissolution capacity e.g. 0.8/0.045 (the solubility of lycopene in oil is ca. 0.045 wt%). Turning to **Fig. 4D**, there is shown the solubilization capacity of the lycopene as a function of the nature

of the surfactant system. As shown, for the case where the surfactant is Tween 60, the efficiency factor (solubilization based on the oil phase) is 0.8 wt%. However, this value is increased to 1.05, 1.1, 1.1 and 1.16 (wt%) for the cases where the surfactant is ethoxylated monoglycerides (EM), triglycerol monooleate (TM), sugar ester (SE), and a mixture of SE + EM, respectively. It should be noted that such efficiency factors are equivalent to a solubilization factor of up to 25 fold.

Fig. 5A shows a phase diagram of a system for solubilizing phytosterol. The system is comprised of an aqueous phase comprising water/propylene glycol in a 1:1 ratio, an oil phase comprising of limonene/ethanol in a 1:1 ratio, and Tween 60 as the surfactant, where the ratio of the surfactant to the oil phase is 3:2 (indicated as the **64** line). It should be noted that the ratio between each of the components of the oil phase to the surfactant is 1:3. The solubility capacity of such a system is given in **Fig. 5B** for a system comprising 1Kg of nano-sized self-assembled structured concentrate. As shown, the maximum solubilization is 165mg, i.e. maximum solubilization is 1.65% (wt) reached at the point where the aqueous phase is 50%. Upon dilution, the solubilization drops as demonstrated by the dilution of the system from 50% water to 80% water. The factor for the dilution is 80/50 = 1.3, while, as can be seen from the figure, the solubilization decrease factor is 165mg/45mg = 3.6 or 0.165/0.045 = 3.6, once again demonstrating that upon dilution, the solubilization factor drops over the dilution factor. Turning to **Fig. 5C**, the efficiency of the solubilization in the described system is represented (α). The efficiency factor, α, is defined as phytosterol/oil(wt/wt)X 100. As shown the maximum solubilization on an oil base is 16.7 wt%. It should be noted that the solubilization decreases as the percentage of the aqueous phase increases. **Fig. 5D** illustrates the solubilization efficiency of phytosterol at different surfactant/oil ratio at two aqueous phase concentrations, 50% and 60%. The efficiency of solubilization of phytosterol increases for both aqueous concentrations as the ratio of the surfactant to oil increases. From Figs 5C and 5D it is apparent that the solubilization factors are 6, 7 for concentrate. Turning to **Fig. 6A** there is shown a phase diagram of a system for solubilizing lutein. The system is comprised of an

aqueous phase comprising water/glycerol in a 3:1 ratio, an oil phase comprising of limonene/ethanol in a 1:2 ratio, and Tween 80 as the surfactant. The ratio of the surfactant to the oil phase may either be 1:1 or 3:2 (indicated as lines **5.5** or **6.4**). It should be noted that such a system might display at different ratios of the components, a two-phase system (demonstrated by the shady area). **Fig. 6B** shows the maximum solubilization that can be achieved with increasing concentration of the aqueous phase in the two systems where the ratio of the oil phase to surfactant may be either 3:2 or 1:1. It is apparent from the findings that the maximum solubilization for the two systems occurs in the bi continuous region (ca. 40 to 60% aqueous solution). For both systems, in the region where oil in water system (O/W) prevails, i.e. where the concentration of the aqueous solution is over 50%, there is limited solubilization. Figs. **6C** and **6D** show the solubilization (capacity) efficiency of lutein ester normalized to the surfactant or oil concentration, respectively, for both 5.5 and 6.4 systems. As shown, solubilization is enhanced as the concentration of the surfactant is increased. Figs. **7A** and **7B** show a comparison of solubilization (capacity) efficiency of lutein ester compared to that of free lutein normalized to the surfactant or oil concentration, respectively, for 6:4 system. The different solubilization profiles of the two compounds demonstrates that their solubilization should be done in different environments. While the free lutein should be solubilized in a water in oil environment (W/O), the ester should be solubilized in a oil in water environment (O/W). As demonstrated in Fig. 2 the nano-sized self-assembled concentrates of the present invention may either be an aqueous phase or an oil phase, thus these two compounds may be solubilized efficiently.

The present invention provides novel nano-sized self-assembled structured concentrates formed by mixing of an oil phase, an aqueous phase and a surfactant. The ternary system forms nano-sized concentrates that are different than those formed by the classical microemulsion concentrate in their size and shape, being in the range of 1.5-80 nM which is 2-3 orders of magnitude lower than that of classical emulsions, microemulsions or self-assembled structured concentrates. The

nano-sized concentrates of the present invention enable in an efficient manner the solubilization, transport and dilution of oil-soluble, oil non-soluble or water-soluble nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates. Thus they may be used as efficient vehicles for transport of active materials into the human body. The capability of these nano-sized self-assembled structured concentrates to solubilize the desired active component exceeds many-fold the solubility capacities of the aqueous or oil phase alone or of the aqueous or oil phase in the presence of an appropriate surfactant. As shown in Figs 4-6 for lycopene, phytosterol and lutein, respectively, the increase is in the range of 7-20 fold. Furthermore, the nano-sized self-assembled structured concentrates, once formed, may be diluted as desired in either oil or water while a single phase is maintained and the nano-sized structured concentrate is intact. The aqueous phase comprises of water, co-surfactants and a polyol co-solvent. The co-surfactant is selected from C_{2-16}-alcohols and C_{2-18} fatty acids. Preferably the alcohols are C_{2-10} where the most preferred are ethanol, propanol, butanol, pentanol, hexanol or heptanol or their mixtures. The fatty acids preferably are C_{2-10} fatty acids. Non-limiting examples of the polyol co-solvent are aldo- or keto-sugars, oligomeric carbohydrates such as glycerol, ethylene glycol, propylene glycol, sorbitol, xylitol, glucose, fructose and the alcohol and polyalcohol are C_1-C_8 and C_2-C_8, respectively. The oil phase is comprised of a solvent and may further comprise a co-solvent. The solvent is selected from the group consisting of C_2-C_6-alcohol, long chain fatty alcohols, C_2-C_7-ketone, C_2-C_7-aldehyde, C_{2-24}-fatty acid or their esters, preferably C_{4-16} fatty acids or their esters, terpene, terpin, terpinene, limonene, penta- or –tetracyclic triterpenic alcohols, sterol, alkylsterol, essential oil, fat soluble lipidic vitamins, fennel oil, ginger oil, lavender oil, eucalyptus oil, anise oil, lemon oil, mandarin oil, peppermint oil, oregano oil, lime oil, tangerine oil, spearmint oil, triethyl citrate, ethyl oleate, ethyl caprylate, anisole, anisyl alcohol, benzyl acetate, benzyl alcohol, benzyl propionate, ethyl lactate, phenethyl alcohol. Terpenes and camphors like α-pinene, borneol, camphour, cineole, carvone, terpineol, menthol, menthone, thymol, geraniol, citral,

terpinolene, hemonene, citronellal. Other natural flavoring materials like linalool, eugenol, vanillin. Synthetic flavoring materials like hexyl alcohol, hexyl aldehyde, benzaldehyde, cinnamic aldehyde, citronellyl butyrate, nerol, phelandrene, phenyl ethyl acetate, ethyl propionate, ethyl laurate, ethyl decanoate, ethyl butyrate, ethyl hexanoate, ethyl caprylate, brandy flavoring oil, apple flavoring oil, almond flavoring oil, paprica flavoring oil, blackberry flavoring oil, blueberry flavoring oil, honey flavoring oil, licorice flavoring oil, maple flavoring oil, strawberry flavoring oil, watermelon flavoring oil. Preferably, the solvent is selected from D-limonene, tocopherol, tocopherol-acetate or triacetin. The co-solvent is selected from the group consisting of fatty acids, fatty alcohols, sterols, terpins, terpenines, essential oils, vitamins, where the co-surfactant may serve as a co-solvent. The at least one surfactant is hydrophilic in nature and non limiting examples are ethoxylated castor oil, ethoxylated sorbitan esters such as ethoxylated sorbitan -monostearate, -monooleate or monolaurate. They may also be sucrose ester, polyglycerol esters such as mono, di, tri, tetra and up to deca (named poly) glycerol (termed polyglycerol) esters of lauric (C_{12}); myristic (C_{14}); palmitic (C_{16}); stearic (C_{18}); oleic ($C_{18:1}$); linoleic ($C_{18:2}$); and their combinations or of any fatty acids (polyglycerol, poly fatty acids) and ethoxylated mono-diglycerides. The hydrophilic nature of the added surfactant should be maintained although its extent may vary by combining two surfactants of different hydrophilic nature or even a hydrophilic surfactant with a hydrophobic surfactant to "dilute" the hydrophilic nature of the former surfactant. In case a hydrophobic surfactant is added it can be of any food grade surfactant, where non-limiting examples are sorbitan esters, sorbitan tristreate, monoglycerides, sucrose esters, ethoxylated castor oils, polyglycerol esters.

Upon the mixture of the above-mentioned components the desired nano-sized structured concentrates form spontaneously with structures having dimensions of 1.5-80 nM, typically 5-20nM. Such nano-sized structured concentrates solubilize in efficient manner lipophilic compounds, as well as hydrophilic compounds. The nanosized-structured concentrates together with the

desired active component comprised therein may be (as shown in **Fig. 2**) in the form of an aqueous continuous phase, an oil continuous phase or a bicontinuous phase. The aqueous continuous phase is comprised of (wt/wt) 0.1 to 40% oil phase, 0.01-40% active matter to be solubilized and 40-99.8% water-soluble matter. An oil continuous phase is comprised of (wt/wt) 0.01-40% water-soluble phase, 0.01-40% active matter to be solubilized and 40-99.8% oil soluble mater. The bi-continuous phase is comprised of (wt/wt) 20-60% oil soluble phase, 0.01-60% active matter to be solubilized and 20-60% water-soluble matter. Lipophilic compounds are non-soluble in aqueous systems and frequently also in food grade organic solvents such as vegetable oils or alcohols. Many of the known nutraceuticals, are lipophilic. Therefore, such compounds are difficult to dissolve or solubilize and therefore their bioavailability and bioefficacy are low. Such lipophilic compounds may be entrapped in appropriate vehicles, which enhance their transport from the guts to the blood stream and further through biological membranes. Micelles (direct and reverse), liposomes, microemulsions and bicontinuous phases are all known. Such vehicles are frequently limited in their use for a particular type of lipophilic compounds. The nano-sized structured concentrates of the present invention overcome such drawback by their versatility and capability to entrap lipophilic moieties and transporting the entrapped material through biological membranes, thus enhancing their bioavailability. The nano-sized structured concentrates of the present invention are isotropic transparent structured fluids, spontaneously formed, thermodynamically stable, of at least two immiscible liquids (water and oil) with the aid of a surfactant, co-surfactant and co-solvent. Their advantage is the large interfacial area that facilitates the solubilization of the lipophilic compounds and the fact they may be fully diluted in water or oil to any desirable dilution maintaining their structure despite the transition from water in oil (W/O) to oil in water (O/W) microenvironment. The nano-sized structured concentrates form a clear and transparent liquid that shows no precipitates, crystalline matter or turbidity. The structured concentrate is of low viscosity, thermodynamically stable, does not separate, coalesce, aggregate, flocculate or

cream at any ambient temperature even after prolonged storage. Additional properties of the novel nanosized structured structured concentrates are protection of the active matter entrapped therein against oxidation, hydrolysis, enzymatic (lipase) and bacterial attack. The nano-sized structured concentrates of the present invention further mask the taste, color and odor of the active material entrapped therein. In a preferred embodiment all the components forming the nano-sized structured concentrates are of food-grade, as the nanosized structured concentrates of the present invention in a preferred mode are used as vehicles for active components to be administered into the human body. The desired active component is trapped within the nanosized structure boundary, where the transition from micellar to O/W to W/O results only in the migration of the active compounds within the nanostructured concentrate (vehicle). The resulting nano-sized self-assembled concentrates after their formation may be diluted as desired in either oil or water. Such versatility of dilutions while maintaining a stable single phase, i.e. retaining a stable solution which does not separate to its constituents has profound implications. The nutraceutical, food supplement, food additive, plant extract, medicament, peptide, protein or carbohydrate may be entrapped in the nano-sized structured concentrate and incorporated into any known food product, medicament, cosmetic preparation solution maintaining its stability.

The invention will now be described by the following non-limiting examples.

Examples

Maximum solubilization of the nutraceuticals, lycopene, phytosterol, flax oil (56% ω-fatty acids), fish oil ((70% ω-fatty acids), Co-Q_{10}, lutein, vitamin D and a mixture of vitamins D and E is given. Solubilization may be done according to the present invention in concentrate (micelle like structure), in water-rich phase, as a bicontinuous phase and in oil-rich phase. The following Tables exemplify the concentrations of the nutraceuticals in each system.

A. Lycopene solubilization

A.1: Micellar concentrate:

Component	Concentration (%)
[1]lycopene	0.05 (and up to 10% oleoresin of tomato or any other oleoresin)
R(+)-limonene	19.8
ethanol	19.8
Tween 60	59.5
PG	0
Water	0

[1]Oleoresin containing 6% of lycopene.

A.2: 30% aqueous phase (W/O nano-sized structures)

Component	Concentration (%)
[1]lycopene (in oleoresin)	0.018
R(+)-limonene	13.96
ethanol	13.96
Tween 60	41.87
PG	14.95
water	14.95

[1]Oleoresin containing 6% of lycopene.

A.3: 70% aqueous phase (O/W nano-sized structures)

Component	Concentration (%)
[1]lycopene	0.042
R(+)-limonene	5.96
ethanol	5.96
Tween 60	17.89
PG	34.79

water	34.79

[1]Oleoresin containing 7% of lycopene.

B. Phytosterol solubilization

It should be noted that solubilization of phytosterol may be done at any level of water (0 to 99%), however the amount of the solubilizate corresponds to its maximum solubilization according to Fig. 5. Furthermore, pure free phytosterol (98%) does not require solubilization in other solvents.

B.1: Oil based composition

Component	**Concentration(%)**	**Component**	**Concentration(%)**
Phytosterols	0.95	Phytosterols	0.85
Monoglycerides	1.5	Monoglycerides	1.2
Canola oil	97.43	Sunflower oil	98.74
Triglycerol monooleate	0.1	lecithins	0.2
vitamineE	0.02	Vitamine E	0.1

B.2: Oil based composition

Component	**Concentration(%)**
Phytosterols	1.1
Monoglycerides	1.4
Soybean oil	97.38
Ethoxylated (40) castor oil	0.1
vitamineE	0.02

B.3: Micellar concentrate

Component	**Concentration (%)**	**Component**	**Concentration (%)**
phytosterol	5.67	phytosterol	1.2

R(+)-limonene	18.6	glycerol	6.0
ethanol	18.6	ethanol	20.0
Tween 60	56.61	Tween 60	59.8
PG	0	Watermelon oil	13

B.4: Micellar concentrate

Component	**Concentration (%)**
phytosterol	1.2
Licorice oil	13.0
ethanol	20.0
Tween 60	54.0
glycerol	6.0

B.5: 30% aqueous phase (W/O nano-sized structures)

Component	**Concentration (%)**	**Component**	**Concentration (%)**
phytosterol	2.91	phytosterol	0.85
R(+)-limonene	13.6	glycerol	4.2
ethanol	13.6	ethanol	14.0
Tween 60	40.77	Tween 60	41.85
PG	14.56	Watermelon oil	9.0
water	14.56	water	30.0

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B.6: 30% aqueous phase (W/O nano-sized structures)

Component	**Concentration (%)**
phytosterol	0.85
glycerol	4.2
ethanol	14.0
Tween 60	41.85
Almond oil	9.0

water	30.0

B.7: 70% aqueous phase (O/W nano-sized structures)

Component	**Concentration (%)**	**Component**	**Concentration (%)**
phytosterol	0.8	phytosterol	0.36
R(+)-limonene	5.95	Watermelon oil	3.9
ethanol	5.95	ethanol	6.0
Tween 60	17.86	Tween 60	17.94
PG	34.72	glycerol	1.8
water	34.72	water	70.0

B.8: 70% aqueous phase (O/W nano-sized structures)

Component	**Concentration (%)**
phytosterol	0.36
Blueberry oil	3.9
ethanol	6.0
Tween 60	17.94
glycerol	1.8
water	70.0

5

C: Co-Q_{10} solubilization

C.1: Micellar concentrate

Component	**Concentration (%)**
Co-Q_{10}	2.45
R(+)-limonene	17.22
ethanol	31.67
Tween 80	48.66

water	0
glycerol	0

C.2: 30% aqueous phase (W/O nano-sized structures)

Component	**Concentration (%)**
Co-Q_{10}	1.04
R(+)-limonene	12.08
ethanol	22.05
Tween 80	35.14
water	22.51
glycerol	7.18

C.3: 70% aqueous phase (O/W nano-sized structures)

Component	**Concentration (%)**
Co-Q_{10}	0.45
R(+)-limonene	5.25
ethanol	9.98
Tween 80	15.28
water	51.78
glycerol	17.26

D. Lutein solubilization

D.1: Micellar concentration (0% aqueous phase)

Component	**Concentration(%)**	**Component**	**Concentration(%)**
D-limonene	13.5	R(+)-limonene	13.16
ethanol	26.4	ethanol	26.32
Tween 80	58.6	Tween 80	58.71
water	0	water	0

glycerol	0	glycerol	0
lutein ester	0.19	free lutein	0.36

D.2: 30% aqueous phase (W/O microemulsion)

Component	**Concentration(%)**	**Component**	**Concentration(%)**
D-limonene	9.06	R(+)-limonene	9.22
ethanol	18.13	ethanol	18.44
Tween 80	40.99	Tween 80	41.67
water	22.97	water	22.37
glycerol	7.65	glycerol	7.45
lutein ester	0.16	free lutein	0.167

D.3: 70% aqueous phase (O/W microemulsion)

Component	**Concentration(%)**	**Component**	**Concentration(%)**
D-limonene	4.1	R(+)-limonene	3.99
ethanol	8.21	ethanol	7.99
Tween 80	18.07	Tween 80	18.23
water	51.94	water	52.28
glycerol	17.31	glycerol	17.42
lutein ester	0.0.47	free lutein	0.0126

5

D.4: Free lutein in a 70% aqueous phase (O/W nano-sized structures)

Component	**Concentration (%)**
D-limonene	1.72
ethanol	13.79
castor oil EO40	15.1
water	52.53
glycerol	17.51

free lutein	0.006

The nanosized structured liquid concentrates can also comprise ratios of other than 1:1 for the water/PG or ethanol/solvent {R(+)-limonene}. The following examples exhibit such systems containing lycopene, phytosterol, lutein ester and free lutein.

E. Lycopene solubilization in a ethanol:solvent ratio of 2:1

70% aqueous phase (O/W)

Component	Concentration (%)
[1]lycopene	0.02
R(+)-limonene	3.98
ethanol	7.97
Tween 60	17.94
PG	34.88
water	34.88

[1]Oleoresin containing 6% lycopene.

F. Phytosterol solubilization in a water:PG ratio of 1:2

70% aqueous phase (O/W)

Component	Concentration (%)
phytosterol	1.0
R(+)-limonene	5.94
ethanol	5.94
Tween 60	17.82
PG	46.2
water	23.1

G. 70% aqueous phase (O/W nano-sized structures) of lutein ester in a solvent:ethanol ratio of 1:3

Component	Concentration (%)
D-limonene	3.08
ethanol	9.23
Tween 80	18.07
water	51.94
glycerol	17.31
lutein ester	0.047

H. 70% aqueous phase (O/W nano-sized structures) of lutein ester in a solvent:ethanol ratio of 1:4

Component	Concentration (%)
D-limonene	2.46
ethanol	9.85
Tween 80	18.07
water	51.94
glycerol	17.31
Lutein ester	0.047

I. Solubilization of Flax oil (56% ω-fatty acids)

I.1: Micellar concentrate

Component	Concentration (%)
Flax oil	0.75
Ethanol	20.0
Medium chain triglycerides	5.0
Triglycerides monooleate	5.0
Vitamin E acetate	0.05
Hydrogenated castor oil	69.2

I.2: 30% water phase (W/O nano-sized structures)

Component	Concentration
Flax oil	0.53
ethanol	14.0
medium chain triglycerides	3.5
triglycerides monooleate	3.5
titamin E acetate	0.035
hydrogenated castor oil	48.44
water	30.0

I.3: 70% water phase (O/W nano-sized structures)

Component	Concentration %
flax oil	0.23
ethanol	6.0
medium chain triglycerides	1.5
triglycerides monooleate	1.5
titamin E acetate	0.015
hydrogenated castor oil	20.76
water	70.0

5

J. Solubilization of Fish oil (70% ω-fatty acids)

J.1: Micellar concentrate

Component	Concentration (%)
fish oil	8.75
ethyl caprylate	9.13
ethanol	18.25
hydrogenated castor oil	63.87

J.2: Micellar concentrate

Component	Concentration (%)
fish oil	1.44
D-limonene	17.36
ethanol	31.97
hydrogenated castor oil	49.22

J.3: 30% water phase (W/O nano-sized structures)

Component	Concentration (%)
fish oil	6.12
ethyl laurate	6.4
ethanol	12.78
hydrogenated castor oil	44.7
water	30.0

J.3: 30% water phase (W/O nano-sized structures)

Component	Concentration (%)
fish oil	1.78
D-limonene	11.94
ethanol	21.76
Tween 80	35.07
water	22.32
Glycerol	7.13

J.5: 90% water phase (O/W nano-sized structures)

Component	Concentration (%)
fish oil	0.05
ethyl caprylate	1.0
ethanol	2.0

hydrogenated castor oil	6.9
water	90.0

K. Solubilization of Vitamin D

K.1: Micellar concentrate

Component	**Concentration (%)**
Tween 80	60.0
Glycerol	5.0
Ethanol	22.0
D-Limonene	12.7
Vitamin D	0.3

K.2: 30% aqueous phase (W/O nano-sized structures)

Component	**Concentration (%)**
Tween 80	42.0
Glycerol	4.1
Ethanol	19.0
D-Limonene	4.7
Vitamin D	0.2
Water	30.0

K.3: 70% water phase (O/W nano-sized structures)

Component	**Concentration (%)**
Tween 80	17.0
Glycerol	1.8
Ethanol	7.3
D-Limonene	3.8
Vitamin D	0.09
Water	70.0

L. Solubilization of Vitamin D and Vitamin E

L.1: Micellar concentrate

Component	Concentration (%)
Tween 60	70.0
Triacetin	7.5
Ethanol	15.0
Vitamin E	7.5
Vitamin D	0.075

L.2: 30% aqueous phase (W/O nano-sized structures)

Component	Concentration (%)
Tween 60	49.0
Triacetin	5.3
Ethanol	10.5
Vitamin E	5.125
Vitamin D	0.075
Water	30.0

L.3: 70% water phase (O/W nano-sized structures)

Component	Concentration (%)
Tween 60	17.0
Triacetin	2.25
Ethanol	4.5
Vitamin E	2.25
Vitamin D	0.023
Water	70.0

CLAIMS:

1. Nano-sized self-assembled structured liquid concentrates comprising of

(i) water;

(ii) a polyol co-solvent selected from the group consisting of alcohols, polyalcohols, aldehydes, ketons, thiols, mono- and –di-saccharides;

(iii) at least one surfactant yielding a surfactant of hydrophilic nature;

(iv) co-surfactant selected from C_{2-16}-alcohols and C_{2-18} fatty acids; and

(v) oil phase being a solvent selected from the group consisting of paraffinic oils selected from hexane, heptane, octane, nonane, decane, undecane, dodecane, tridecane, tetradecane, pentadecane, hexadecane, heptadecane, octadecane; silicone oils; long chain fatty alcohols C_{5-18}, C_{2-12}-ketone, preferably C_{2-7}-ketone, C_{2-12}-aldehyde, preferably C_{2-7}-aldehyde, C_{2-24}-fatty acid or their esters, glycerol mono, di and tri-esters, terpene, terpin, terpinene, limonene, penta- or –tetracyclic triterpenic alcohols, sterol, alkylsterol, essential oil oleoresins, fat soluble lipidic vitamins, fennel oil, ginger oil, lavender oil, eucalyptus oil, anise oil, lemon oil, mandarin oil, peppermint oil, oregano oil, lime oil, tangerine oil, spearmint oil, triethyl citrate, ethyl oleate, ethyl caprylate, anisole, anisyl alcohol, benzyl acetate, benzyl alcohol, benzyl propionate, ethyl lactate, phenethyl alcohol, terpenes and camphors selected from α-pinene, borneol, camphour, cineole, carvone, terpineol, menthol, menthone, thymol, geraniol, citral, terpinolene, hemonene, citronellal, natural flavoring materials selected from linalool, eugenol, vanillin, synthetic flavoring materials selected from hexyl alcohol, hexyl aldehyde, benzaldehyde, cinnamic aldehyde, citronellyl butyrate, nerol, phelandrene, phenyl ethyl acetate, ethyl propionate, ethyl laurate, ethyl decanoate, ethyl butyrate, ethyl hexanoate, ethyl caprylate, brandy flavoring oil, apple flavoring oil, almond flavoring oil, paprica flavoring oil, blackberry flavoring oil, blueberry flavoring oil, honey flavoring oil,

licorice flavoring oil, maple flavoring oil, strawberry flavoring oil, watermelon flavoring oil wherein said solvent may further comprise at least one co-solvent selected from fatty acids, fatty alcohols, sterols, terpins, terpenines, essential oils, vitamins.

2. Nano-sized self-assembled structured liquid concentrates according to claim 1, wherein said at least one surfactant is food grade surfactant and is selected from the group consisting of ethoxylated castor oil, ethoxylated sorbitan esters selected from ethoxylated sorbitan -monostearate, -monooleate, monolaurate, sucrose esters, polyglycerol esters selected from mono, di, tri, tetra up to deca glycerol, esters of lauric (C_{12}); myristic (C_{14}); palmitic (C_{16}); stearic (C_{18}); oleic ($C_{18:1}$); linoleic ($C_{18:2}$) acids, combinations of fatty acids and ethoxylated mono-diglycerides, or mixtures thereof.

3. Nano-sized self-assembled structured liquid concentrates according to claim 1, wherein the polyol co-solvent is selected from the group of aldo- or keto-sugars, oligomeric carbohydrates or an alcohol and polyalcohol selected from C_1-C_8 and C_2-C_8, respectively.

4. Nano-sized self-assembled structured liquid concentrates according to claim 1, wherein said oil phase being a solvent is selected from the group consisting of limonene, tocopherol, tocopherol-acetate, or triacetin.

5. Nano-sized self-assembled structured liquid concentrates comprising of

(i) Water;

(ii) a polyol co-solvent selected from the group consisting of alcohols, polyalcohols, aldehydes, ketons, thiols, mono- and –di-saccharides;

(iii) at least one surfactant yielding a surfactant of hydrophilic nature;

(iv) co-surfactant selected from $C_{2\text{-}16}$-alcohols and $C_{2\text{-}18}$ fatty acids; and

(v) oil phase being a solvent selected from the group consisting of paraffinic oils selected from hexane, heptane, octane, nonane, decane, undecane, dodecane, tridecane, tetradecane, pentadecane, hexadecane, heptadecane, octadecane; silicone oils; long chain fatty alcohols $C_{5\text{-}18}$, $C_{2\text{-}12}$-ketone, preferably $C_{2\text{-}7}$-ketone, $C_{2\text{-}12}$-aldehyde, preferably

C_{2-7}-aldehyde, C_{2-24}-fatty acid or their esters, glycerol mono, di and tri-esters, terpene, terpin, terpinene, limonene, penta- or –tetracyclic triterpenic alcohols, sterol, alkylsterol, essential oil oleoresins, fat soluble lipidic vitamins, fennel oil, ginger oil, lavender oil, eucalyptus oil, anise oil, lemon oil, mandarin oil, peppermint oil, oregano oil, lime oil, tangerine oil, spearmint oil, triethyl citrate, ethyl oleate, ethyl caprylate, anisole, anisyl alcohol, benzyl acetate, benzyl alcohol, benzyl propionate, ethyl lactate, phenethyl alcohol, terpenes and camphors selected from α-pinene, borneol, camphour, cineole, carvone, terpineol, menthol, menthone, thymol, geraniol, citral, terpinolene, hemonene, citronellal, natural flavoring materials selected from linalool, eugenol, vanillin, synthetic flavoring materials selected from hexyl alcohol, hexyl aldehyde, benzaldehyde, cinnamic aldehyde, citronellyl butyrate, nerol, phelandrene, phenyl ethyl acetate, ethyl propionate, ethyl laurate, ethyl decanoate, ethyl butyrate, ethyl hexanoate, ethyl caprylate, brandy flavoring oil, apple flavoring oil, almond flavoring oil, paprica flavoring oil, blackberry flavoring oil, blueberry flavoring oil, honey flavoring oil, licorice flavoring oil, maple flavoring oil, strawberry flavoring oil, watermelon flavoring oil, wherein said solvent may further comprise at least one co-solvent selected from fatty acids, fatty alcohols, sterols, terpins, terpenines, essential oils, vitamins;

loaded with oil soluble, oil non-soluble or water soluble material selected from the group consisting of nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates.

6. Nano-sized self-assembled structured liquid concentrates according to claim 5, wherein said surfactant is food grade and is selected from the group consisting of ethoxylated castor oil, ethoxylated sorbitan esters selected from ethoxylated sorbitan -monostearate, -monooleate, monolaurate, sucrose esters, polyglycerol esters selected from mono, di, tri, tetra up to deca glycerol, esters of lauric (C_{12}); myristic (C_{14}); palmitic (C_{16}); stearic (C_{18}); oleic ($C_{18:1}$); linoleic ($C_{18:2}$)

acids, combinations of fatty acids and ethoxylated mono-diglycerides, or mixtures thereof.

7. Nano-sized self-assembled structured liquid concentrates according to claim 5, wherein the polyol co-solvent is selected from the group of aldo- or keto-sugars, oligomeric carbohydrates or an alcohol and polyalcohol selected from C_1-C_8 and C_2-C_8, respectively.

8. Nano-sized self-assembled structured liquid concentrates according to claim 5, wherein said solvent is selected from the group consisting of limonene, tocopherol, tocopherol-acetate or triacetin.

9. Nano-sized self-assembled structured liquid concentrates according to claim 5, wherein said nutraceuticals are selected from the group comprising of lutein, lutein esters, β-carotene, lycopene, Co-Q_{10}, flax seed oil, fish oil, lipoic acid, vitamin B_{12}, vitamin D, vitamin E, α- and γ-polyunsaturated fatty acids, phytosterols or their mixtures.

10. A nano-sized self-assembled structured liquid concentrates according to claim 5 in the form of aqueous continuous phase comprising of (wt/wt) 0.1 to 40% oil phase, 0.01-40% solubilized matter selected from oil-soluble, oil non-soluble or water-soluble nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates and 40-99.8% water-soluble matter.

11. A nano-sized self-assembled structured liquid concentrates according to claim 5 in the form of oil continuous phase comprising of (wt/wt) 0.01-40% water-soluble phase, 0.01-40% solubilized matter selected from oil-soluble, oil non-soluble or water-soluble nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates and 40-99.8% oil soluble matter.

12. A nano-sized self-assembled structured liquid concentrates according to claim 5 in the form of bicontinuous phase comprising of (wt/wt) 20-60% oil soluble phase, 0.01-60% solubilized matter selected from oil-soluble, oil non-soluble or water-soluble nutraceuticals, food supplements, food additives, plant

extracts, medicaments, peptides, proteins or carbohydrates and 20-60% water soluble matter.

13. Food product, medicament, cosmetic preparation comprising nano-sized self-assembled structured liquid concentrates in the form of an aqueous continuous phase according to claim 10.

14. Food product, medicament, cosmetic preparation comprising nano-sized self-assembled structured liquid concentrates in the form of oil continuous phase according to claim 11.

15. Food product, medicament, cosmetic preparation comprising nano-sized self-assembled structured liquid concentrates in the form of a bi continuous phase according to claim 12.

16. Nano-sized self-assembled structured liquid concentrates in the form of an aqueous continuous phase according to claim 10 for use in enhancing bioavailability of said oil-soluble, oil non-soluble or water-soluble nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates.

17. Nano-sized self-assembled structured liquid concentrates in the form of an oil continuous phase according to claim 11 for use in enhancing bioavailability of said oil-soluble, oil non-soluble or water-soluble nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates.

18. Nano-sized self-assembled structured liquid concentrates in the form of an bicontinuous phase according to claim 12 for use in enhancing bioavailability of said oil-soluble, oil non-soluble or water-soluble nutraceuticals, food supplements, food additives, plant extracts, medicaments, peptides, proteins or carbohydrates.

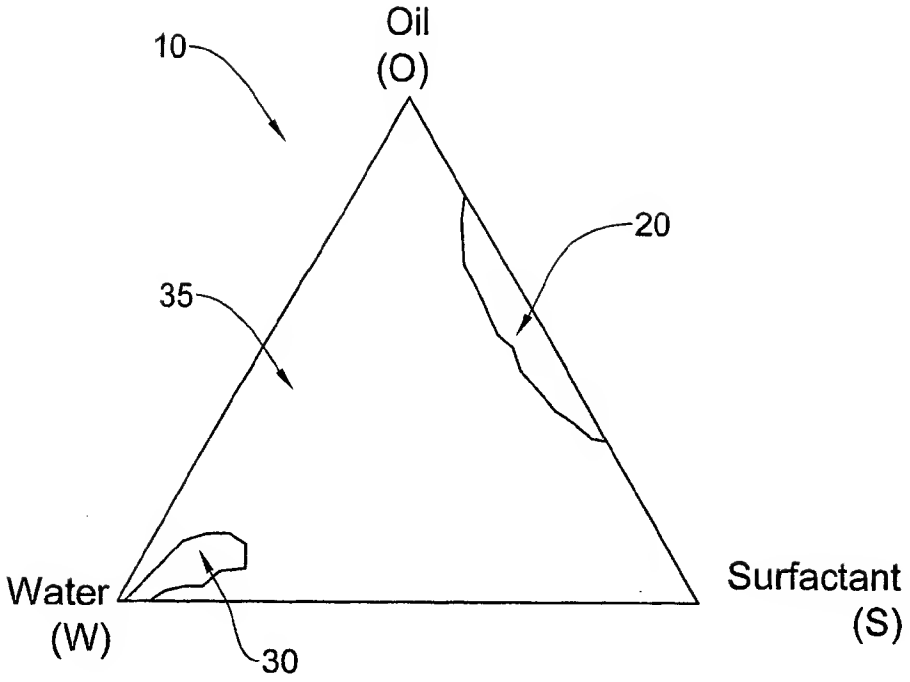
Oil
(O)
10
20
35
Water
(W)
30
Surfactant
(S)

FIG. 1A

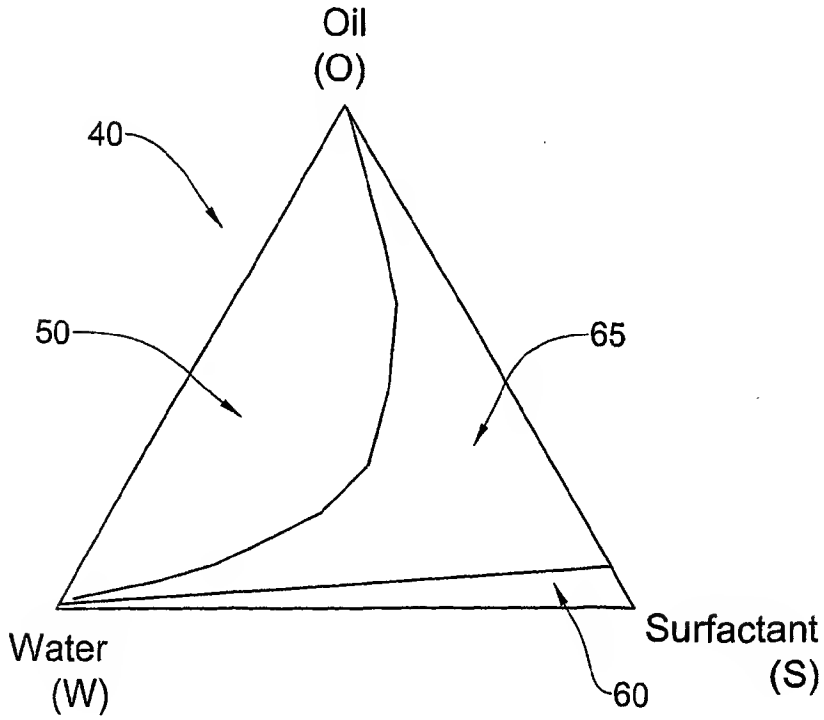
Oil
(O)
40
50
65
Water
(W)
60
Surfactant
(S)

FIG. 1B

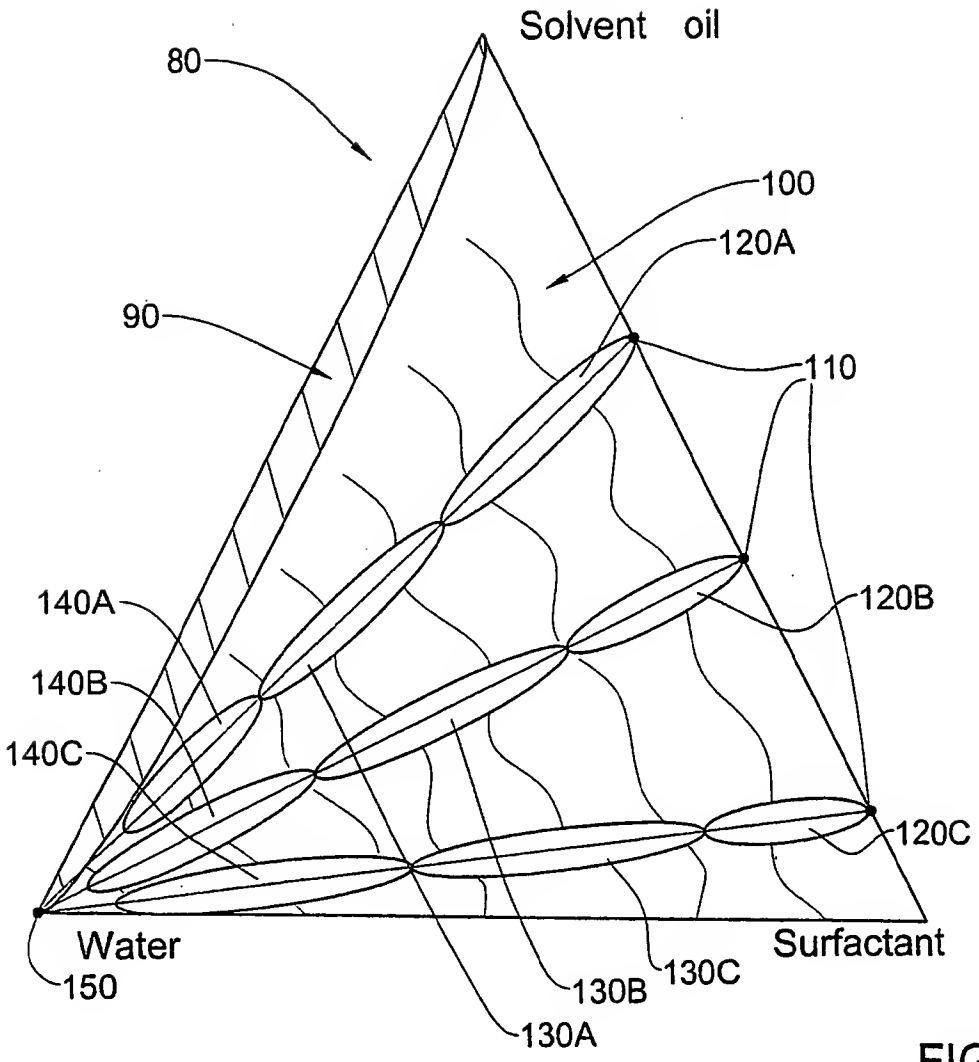
Solvent oil
80
100
120A
90
110
120B
140A
140B
140C
120C
Water
150
Surfactant
130B
130C
130A

FIG. 2

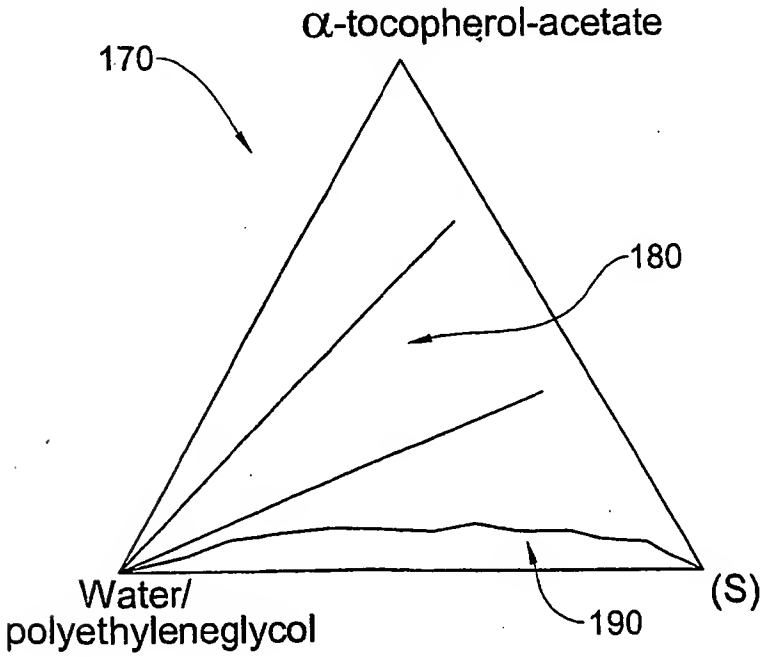
α-tocopherol-acetate
170
180
Water/
polyethyleneglycol
190
(S)

FIG. 3

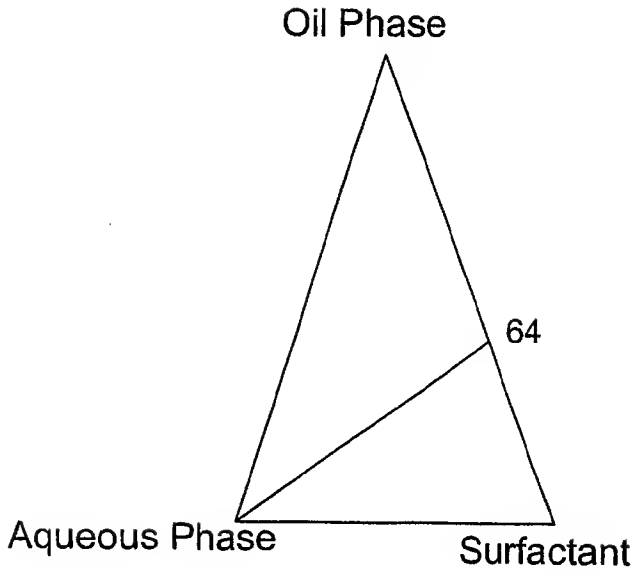
Oil Phase
64
Aqueous Phase
Surfactant

FIG. 4A

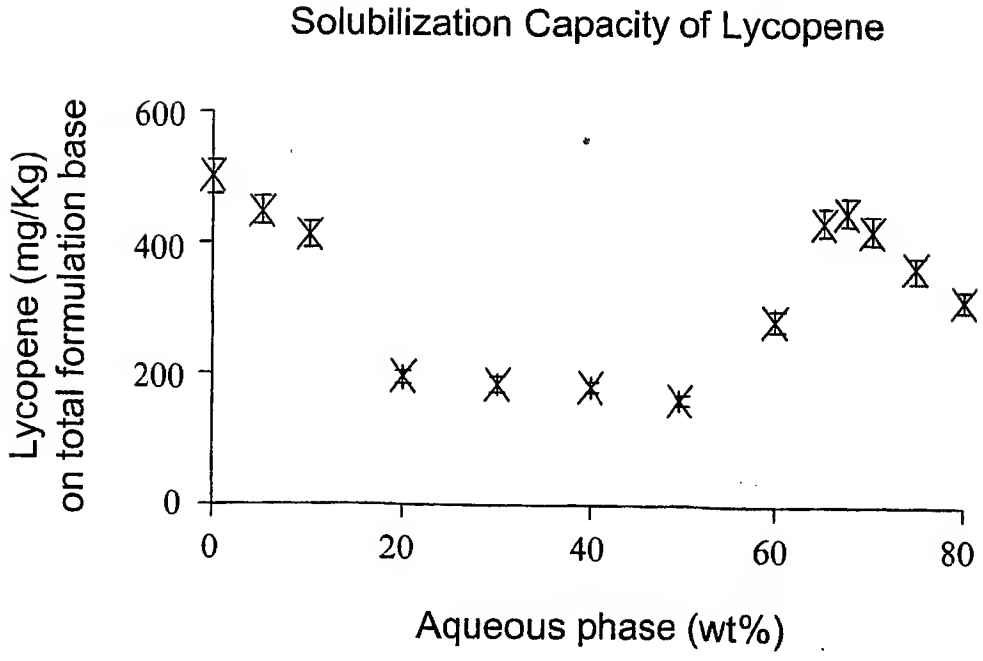
Solubilization Capacity of Lycopene
Lycopene (mg/Kg) on total formulation base
600
400
200
0
0
20
40
60
80
Aqueous phase (wt%)

FIG. 4B

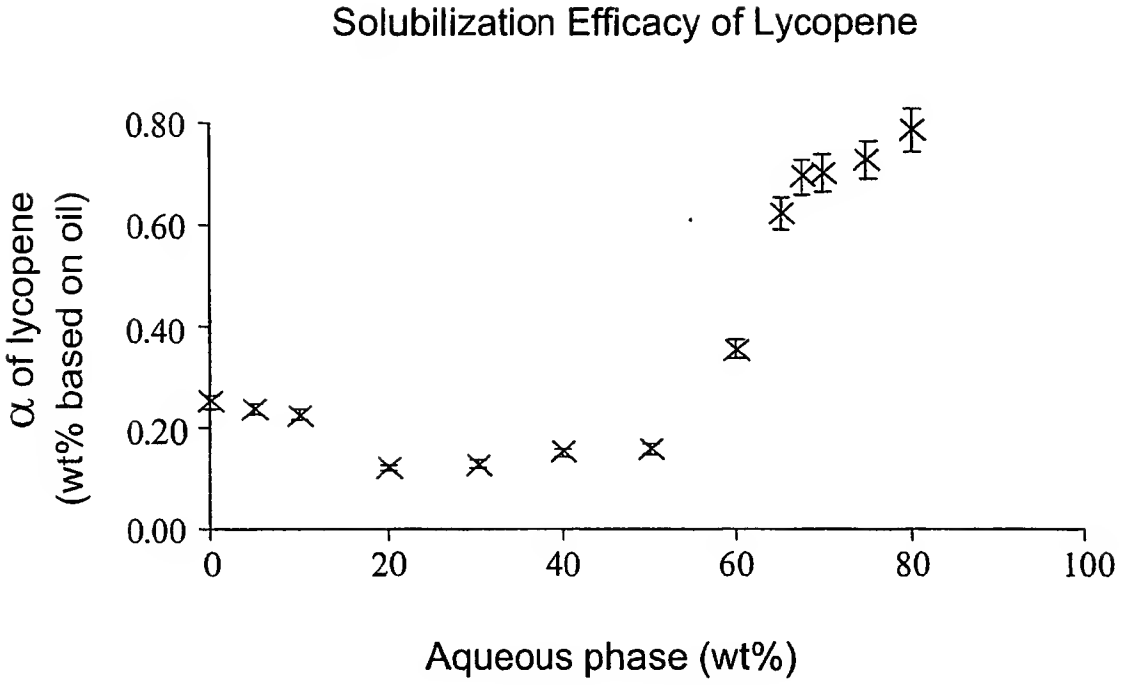

FIG. 4C

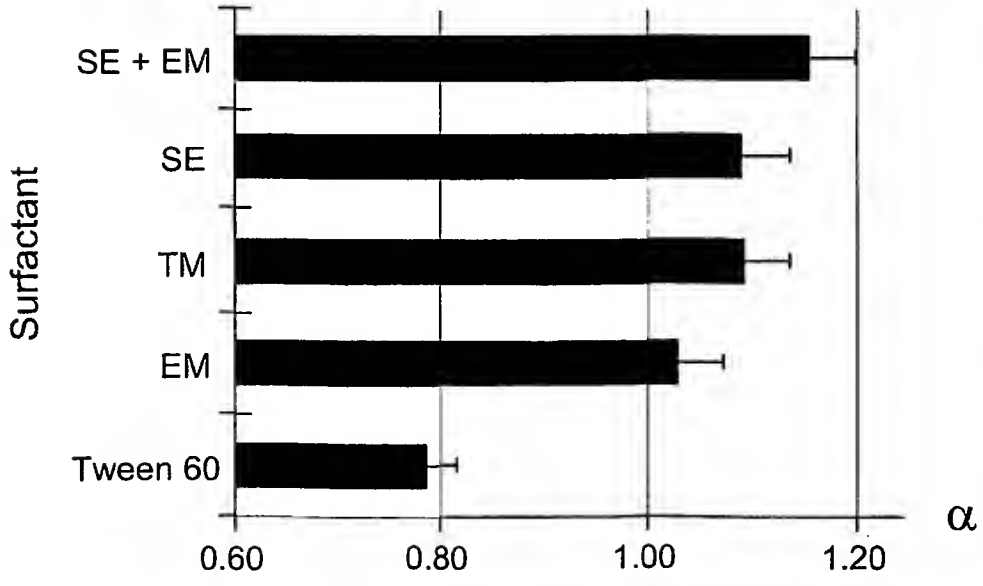

FIG. 4D

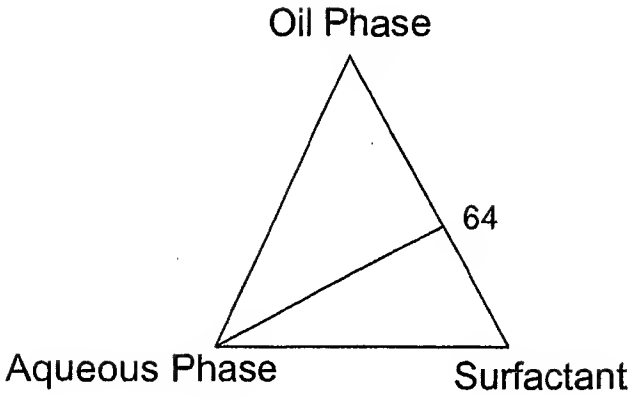
Oil Phase
64
Aqueous Phase
Surfactant

FIG. 5A

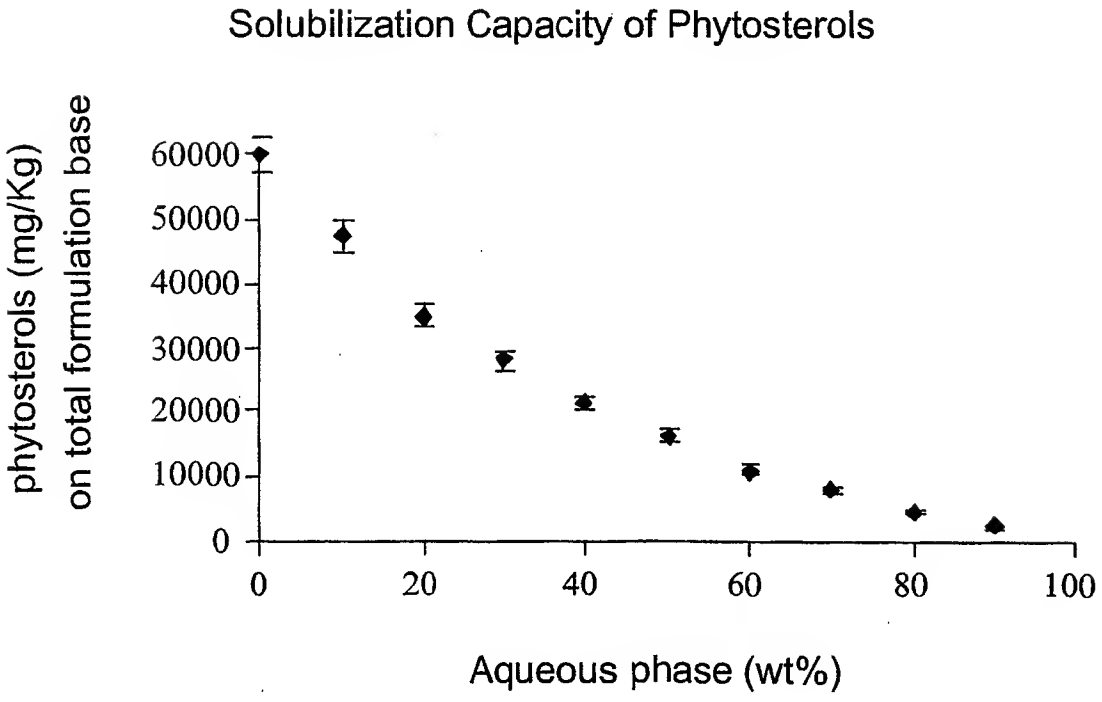
Solubilization Capacity of Phytosterols
phytosterols (mg/Kg)
on total formulation base
60000
50000
40000
30000
20000
10000
0
0
20
40
60
80
100
Aqueous phase (wt%)

FIG. 5B

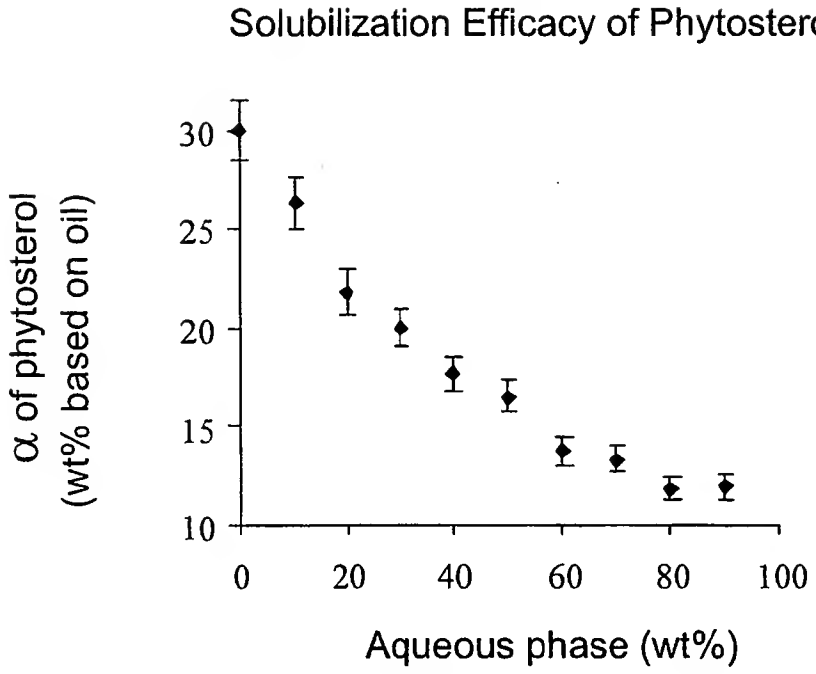
Solubilization Efficacy of Phytosterols
α of phytosterol (wt% based on oil)
30
25
20
15
10
0
20
40
60
80
100
Aqueous phase (wt%)

FIG. 5C

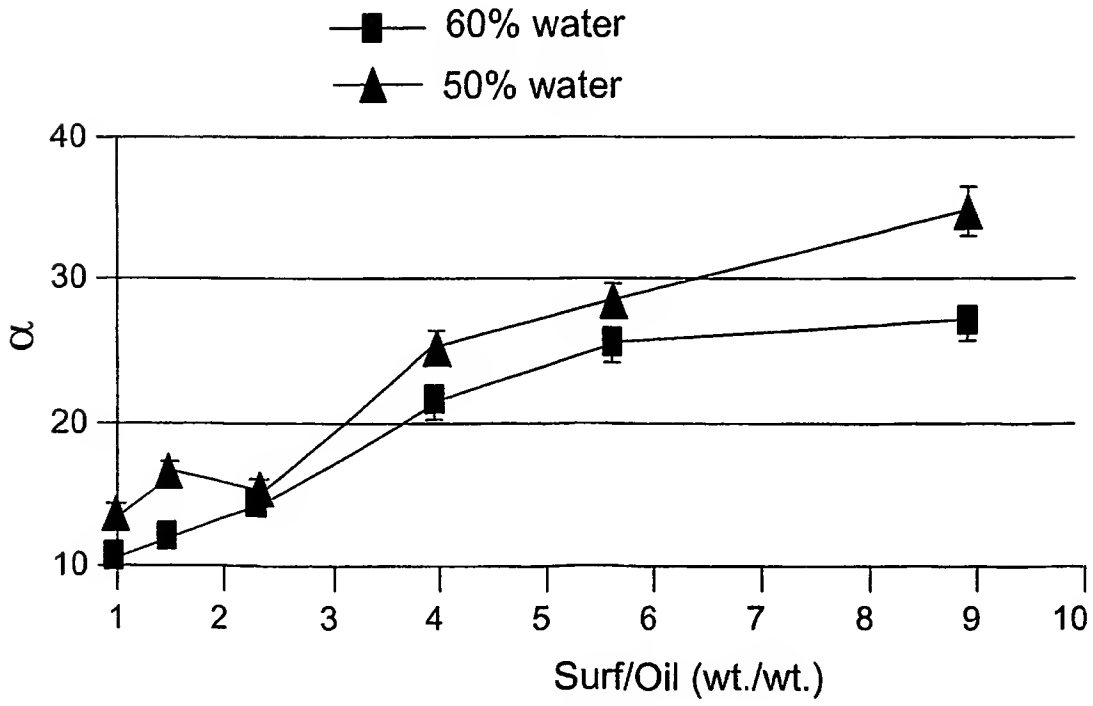
60% water
50% water
40
30
20
10
α
1
2
3
4
5
6
7
8
9
10
Surf/Oil (wt./wt.)

FIG. 5D

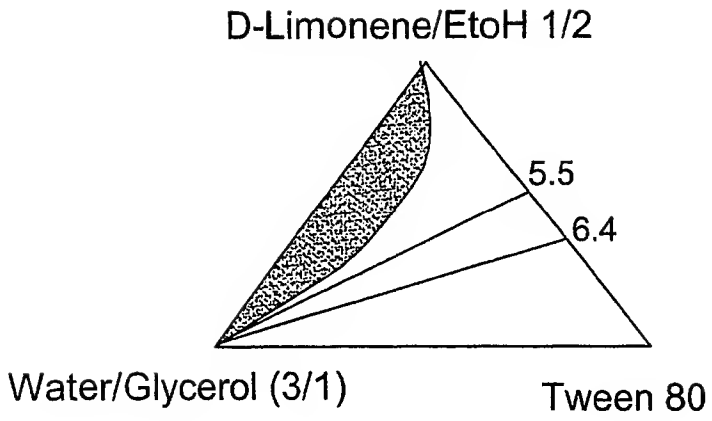
D-Limonene/EtoH 1/2
5.5
6.4
Water/Glycerol (3/1)
Tween 80

FIG. 6A

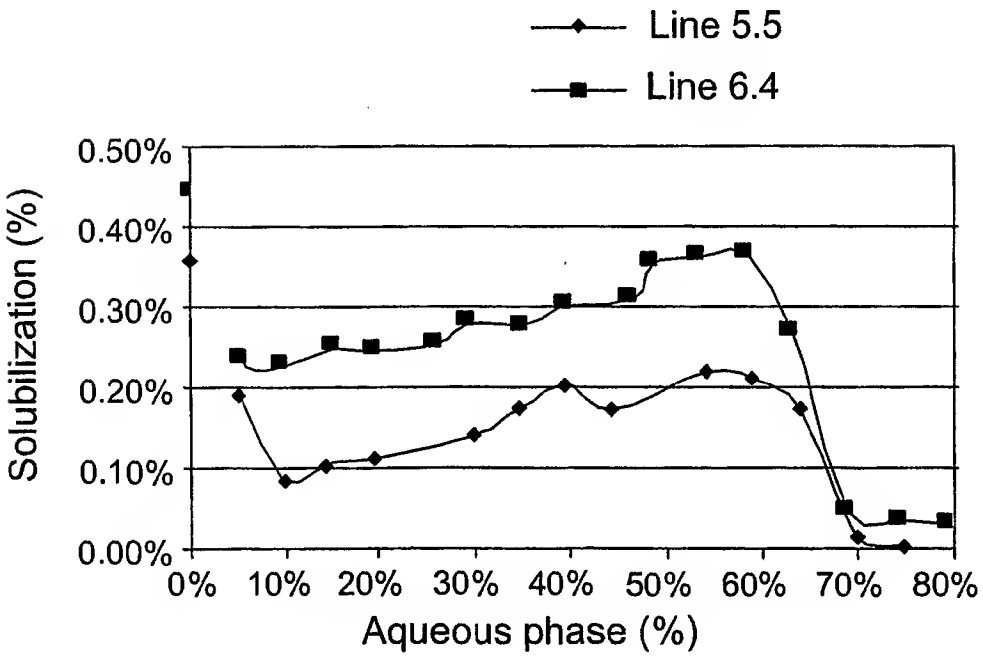
Line 5.5
Line 6.4
Solubilization (%)
0.50%
0.40%
0.30%
0.20%
0.10%
0.00%
0% 10% 20% 30% 40% 50% 60% 70% 80%
Aqueous phase (%)

FIG. 6B

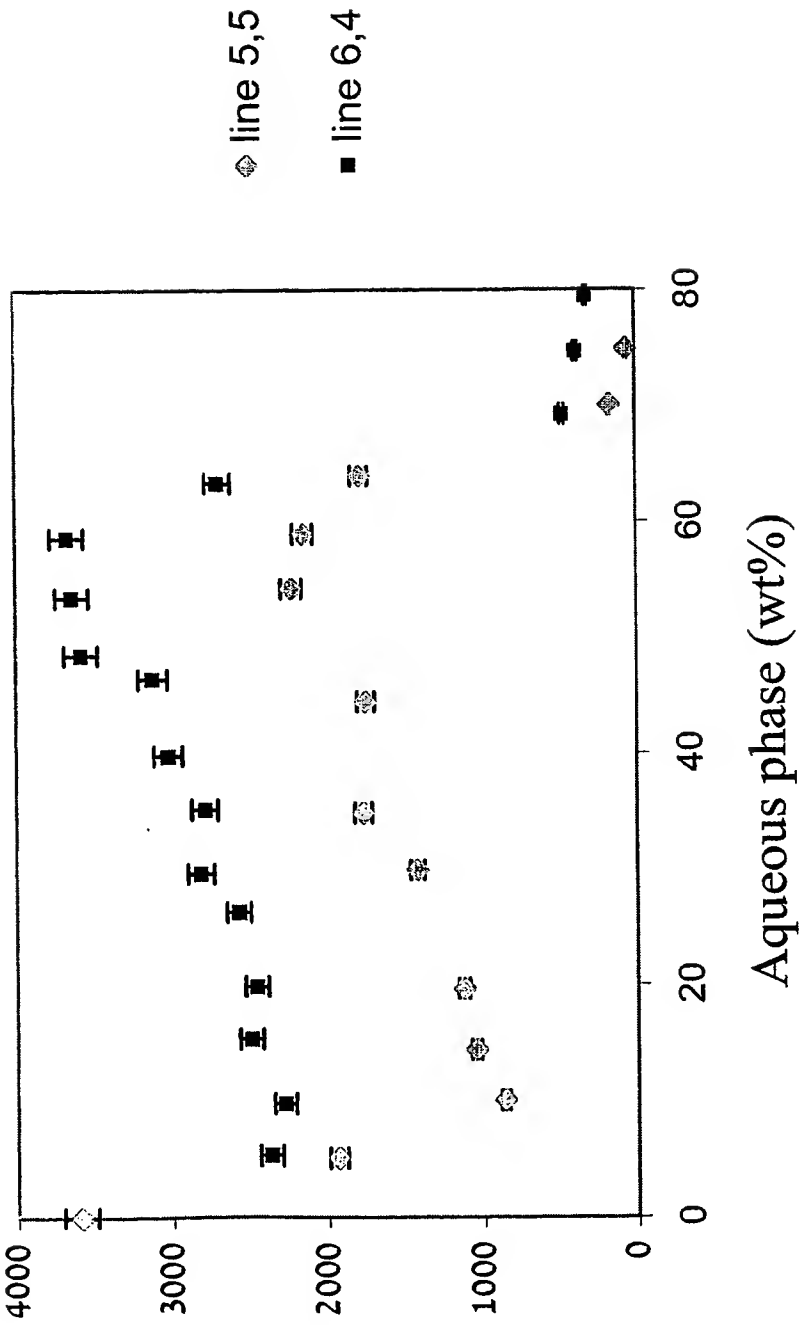
line 5,5
line 6,4
Lutein (mg/ Kg)
on total formulation base
4000
3000
2000
1000
0
0
20
40
60
80
Aqueous phase (wt%)

FIG.6C

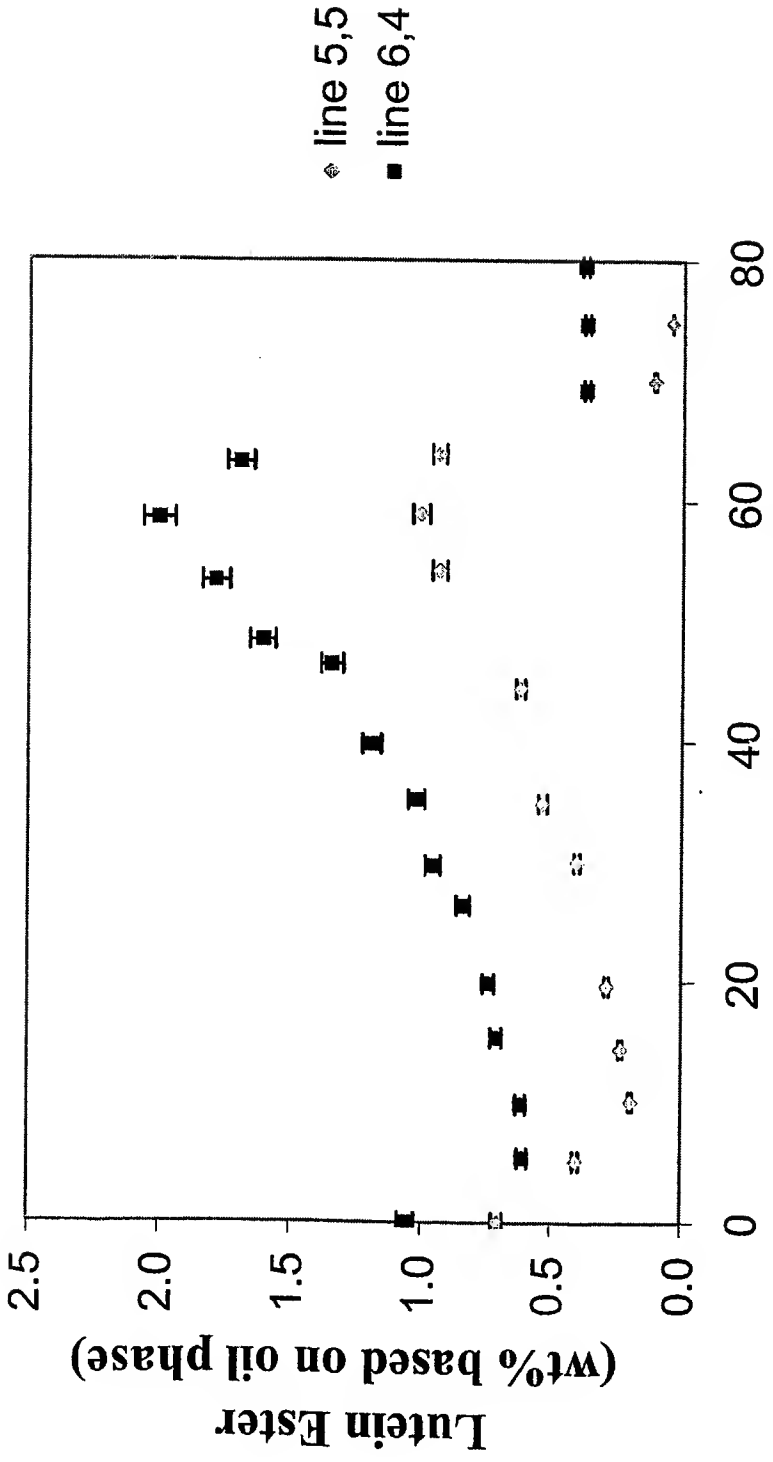
line 5,5
line 6,4
Lutein Ester
(wt% based on oil phase)
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
Aqueous phase (wt%)

FIG.6D

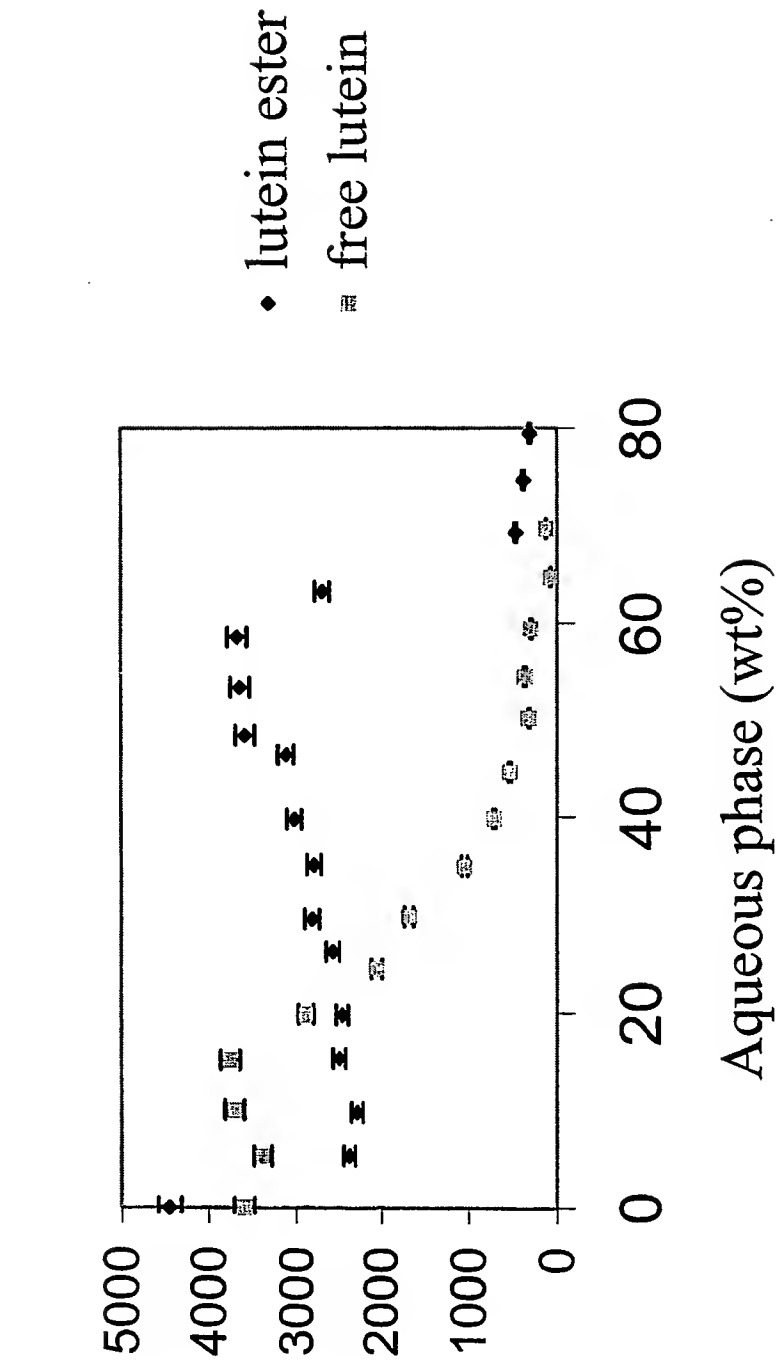
lutein ester
free lutein
Lutein (mg/Kg)
on total formulation base
5000
4000
3000
2000
1000
0
0
20
40
60
80
Aqueous phase (wt%)

FIG.7A

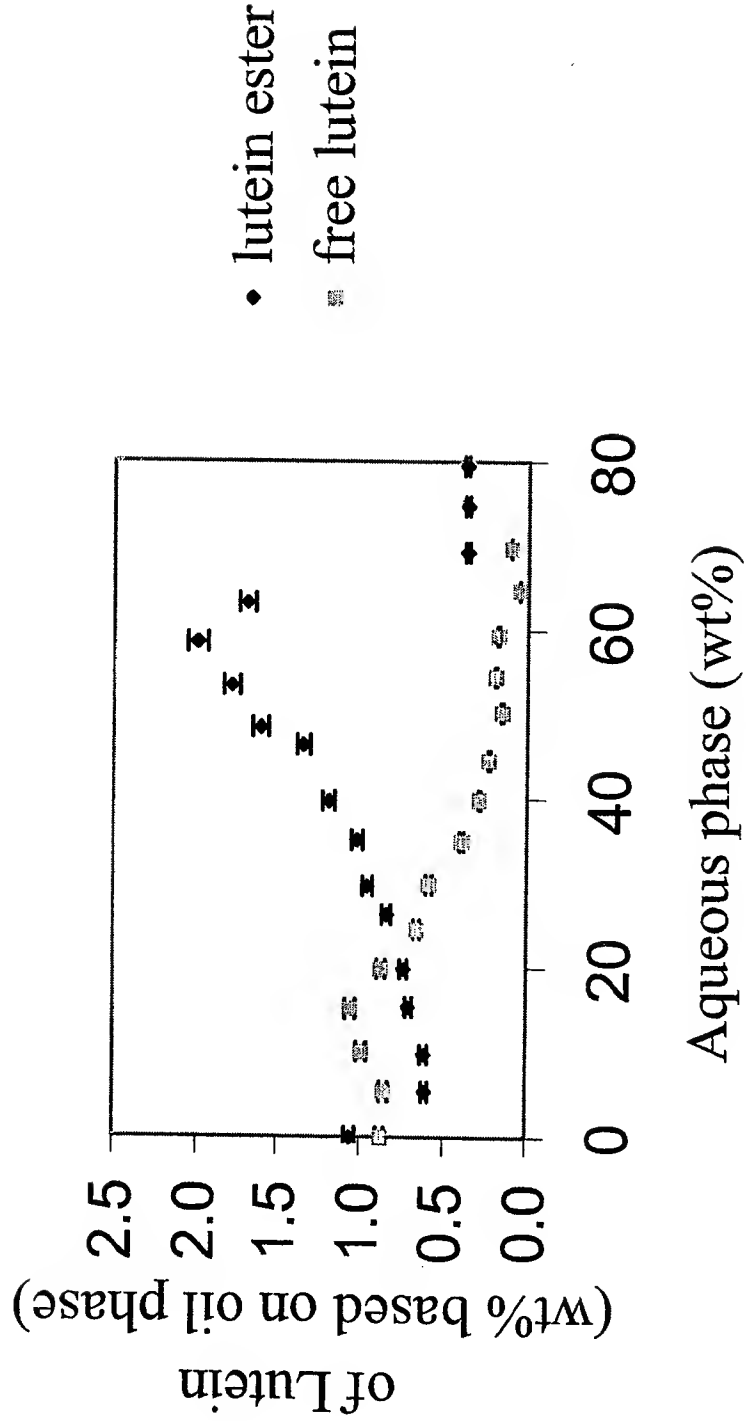
lutein ester
free lutein
of Lutein
(wt% based on oil phase)
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
Aqueous phase (wt%)

FIG.7B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 03/00498

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/30 A23L1/302 A23L1/303 A61K9/107 A23L1/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 010 416 A (OREAL) 21 June 2000 (2000-06-21) examples 1,2 page 2, paragraphs 1-3,9-12 page 3, paragraphs 15-22 page 5, paragraphs 32-35,40,41 claims 1,3,5-8,11,15-17,21 ---	1-18
X	WO 99 06043 A (MOROZOWICH WALTER ;UPJOHN CO (US); GAO PING (US)) 11 February 1999 (1999-02-11) example 16 page 1, line 5-7 page 5, line 10-36 page 6, line 22 -page 8, line 30; claims 1,3,15,17,20 ---	1-18
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 September 2003	07/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Tallgren, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 03/00498

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 09764 A (BYRON BASSETT LTD ;RAZZAK MAJID HAMEED ABDUL (NZ); TUCKER IAN GEOR) 7 February 2002 (2002-02-07) claims 1-5,8-11; example 3; tables 1,2 page 1, line 21-25 page 2, line 29 -page 3, line 32 page 4, line 5-27 ---	1-18
A	WO 01 37808 A (LIPOCINE INC) 31 May 2001 (2001-05-31) page 1, line 5-25 page 6, line 5 -page 65, line 13 examples 1-5,13-28 & US 6 248 363 A (LIPOCINE INC) 19 June 2001 (2001-06-19) cited in the application ---	1-18
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		BR 9810866 A	26-09-2000
		BR 9811058 A	05-09-2000
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		ES 2174462 T3	01-11-2002
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 03/00498

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